FORM PTO-1390 (REV. 6-87)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 1038-02

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/05690	24 AUGUST 2000 (24.08.00)	24 AUGUST 1999 (24.08.99)

TITLE OF INVENTION
REMEDIES FOR NEUROPATHIC PAIN AN MODEL ANIMALS OF NEUROPATHIC PAIN

APPLICANT(S) FOR DO/EO/US
Hiroshi Nagase, Takashi Endo, Kuniaki Kawamura, Toshiaki Tanaka, Tomohiko Suzuki, Tsutomu Suzuki, Yasushi Kuraishi and Kimiyasu Shiraki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

1. ■ This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

2. ■ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS	9 -20=	0	x $18 00	$
	INDEPENDENT CLAIMS	2 -3=	0	x $84 00	
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280 00	
	BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)):				
	☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) $710.00				
	☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $740 00				
	☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,040.00				
	☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2) to (4) ..... $ 100 00				
	■ International Search Report enclosed $890.00				$890.00
	Surcharge of $_____ for furnishing the National fee or oath or declaration later than ☐20 ☐30 mos from the earliest claimed priority date (37 CFR 1.482(e)). $130.00				
				TOTAL OF ABOVE CALCULATIONS	$890 00
	Reduction by ½ for filing by small entity, if applicable. Affidavits must be filed also. (Note 37 CFR 1 9, 1 27, 1.28)				
				SUBTOTAL	$890 00
	Processing fee of $_____ for furnishing the English Translation later than ☐20 ☐30 mos from the earliest claimed priority date (37 CFR 1.482(f)) $130.00				
				TOTAL NATIONAL FEE	
	Fee for recording the enclosed assignment (37 CFR 1.21(h)). $40.00				+
				TOTAL FEES ENCLOSED	$890 00

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3405 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3405. A duplicate copy of this sheet is enclosed.

3. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
   c. ■ has been transmitted by the International Bureau.

4. ■ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

5. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.

6. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

7. ☐ An oath or declaration of the inventor (35 U.S.C. 371(c)(4)).

8. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Other document(s) or information included:

9. ☐ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

10. ☐ An Assignment document for recording and a Recordation Form Cover Sheet - Patents Only. Please mail the recorded assignment document to the person whose signature, name and address appears at the bottom of this page.

11. The above checked items are being transmitted
   a. ☐ before the 18th month publication.
   b. ☐ after publication and the Article 20 communication but before 20 months from the priority date.
   c. ☐ after 20 months but before 22 months (surcharge and/or processing fee included).
   d. ☐ after 22 months (surcharge and/or processing fee included).
      Note: Petition to revive (37 C.F.R. 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 22 months *and no proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.*
   e. ■ by 30 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
   f. ☐ after 30 months but before 32 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date (surcharge and/or processing fee included).
   g. ☐ after 32 months (surcharge and/or processing fee included).
      Note: Petition to revive (37 C.F.R. 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 32 months and a proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.

12. At the time of transmittal, the time limit for amending claims under Article 19
   a. ☐ has expired and no amendments were made.
   b. ☐ has not yet expired.

13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

SCHNADER HARRISON SEGAL & LEWIS

Date: 12 Feb 2002

By: _____

T. Daniel Christenbury, Reg. No. 31,750
1600 Market Street, 36th Floor
Philadelphia, PA 19103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	
Examiner	:	
Serial No.	:	
Filed	: Herewith	
PCT No.	: PCT/JP00/05690	
PCT Filed	: August 24, 2000	
Inventors	: Hiroshi Nagase	Docket: 1038-02
	: Takashi Endo	
	: Kuniaki Kawamura	
	: Toshiaki Tanaka	
	: Tomohiko Suzuki	Confirmation. No.:
	: Tsutomu Suzuki	
	: Yasushi Kuraishi	
	: Kimiyasu Shiraki	
Title	: REMEDIES FOR	
	: NEUROPATHIC PAIN	
	: AND MODEL ANIMALS	
	: OF NEUROPATHIC PAIN	

Dated: February 12, 2002

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, DC 20231

Sir:

Prior to action on the merits of the case, kindly amend the above-identified application as follows:

In the Specification (Clean copy as amended)

Please replace the paragraph bridging between pages 18-20 with the following:

When the compounds represented by the general formula (I) are used as therapeutic agents for neuropathic pain, the compounds can be used alone or in combination with other compounds represented by the general formula (I) as active ingredients. After the compounds are purified and pass the necessary stability test, the compounds can be orally or parenterally administered as they are, or as pharmaceutical compositions mixed with know, pharmacologically acceptable acids, carrier, excipients, etc. Examples of

administration modes include injections, orally administered drugs, such as tablets, capsules, granules, powdered drugs, and syrups, and administration per rectum by suppositories. The content of the active ingredient in the therapeutic agent for neuropathic pain of the present invention is preferably 1 to 90% by weight, and more preferably, 30 to 70% by weight. Although the dosage is appropriately selected depending on the symptoms, age, body weight, administration modes, etc., the dose per day for an adult is 0.0001 mg to 1 g in the case of injections, and 0.005 mg to 10 g in the case of orally administered drugs, and administration can be performed once or several times a day. Additionally, various adjuvants may be mixed therewith in order to improve the therapeutic effects on neuropathic pain. Furthermore, the therapeutic agents of the present invention may be combined with known drugs used for treating pain. Examples of drugs which can be combined with the therapeutic agent include, but are not particularly limited to, antidepressants, antianxiety agents, anticonvulsants, topical anesthetics, sympathetic agents, NMDA-receptor antagonists, calcium channel blockers, serotonin receptor antagonists, GABA-receptor activators, opioid agonists, and antiinflammatory agents. More specifically, the examples are amitriptyline, imipramine, desipramine, fluoxetine, carbamazepine, diazepam, gabepentin, valproic acid, lidocaine, clonidine, phentolamine, prazosin, ketamine, ifenprodil, dextromethorphan, mexiletine, ketanserin, sarpogrelate hydrochloride, benzodiazepine, barbiturate, tramadol, fentanyl, and dicrofenac. Furthermore, in the case of treatment for neuropathjc pain caused by virus infection, antiviral agents, such as aciclovir and famciclovir, can be combined with the therapeutic agent of the present invention. In addition, nerve block therapy, acupuncture, actinotherapy, epidural electro-stimulation therapy, etc. that are used for treatment of neuropathic pain can be combined with the therapeutic agent of the present invention.

Please replace the paragraph bridging between pages 22-23 with the following:

In the compound, which is used for making the animal model, represented by general formula (II), preferably, R^1 is hydrogen, an alkyl group having 1 to 5 carbon atoms, a cycloalkylmethyl group having 4 to 7 carbon atoms, a cycloalkenylmethyl group having 5 to 7 carbon atoms, a phenyl group, a naphthyl group, a phenylaralkyl group having 7 to 13 carbon atoms, an alkenyul group having 3 to 7 carbon atoms, a furan-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophene-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms); R^2 is hydrogen, a hydroxy group, an acetoxy group, a propionyloxy group, a methoxy group, or an ethoxy group; R^3 is hydrogen, a hydroxy group, an acetoxy group, a propionyloxy group, a methoxy group, and ethoxy group, or a benzyloxy group; X is CH; m is an integer from 0 to 2; and R^4 is independently fluoro, chloro, bromo, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a nitro group, or an amino group. More preferably, R^1 is hydrogen, a methyl group, an ethyl group, a cyclopropylmethyl group, a cyclobutylmethyl group, a cyclopentylmethyl group, a cyclopentenylmethyl group, a cyclohexenylmethyl group, a benzyl group, a phenethyl group, a trans-2-butenyl group, a 3-methyl-2-butenyl group, an allyl group, a furan-2-yl-methyl group, or a thiophene-2-yl-methyl group; R^2 is hydrogen, a hydroxy group, an acetoxy group, or a methoxy group; R^3 is hydrogen, a hydroxy group, an acetoxy group, a methoxy group, or a benzyloxy group; X is CH; m is an integer from 0 to 2; an integer m of R^4 is independently fluoro, chloro, bromo, a methyl group, a methoxy group, a nitro group, or an amino group.

In the Claims (clean copy as amended)

4. (Amended) A therapeutic agent for neuropathic pain according to Claim 1, wherein said neuropathic pain is pain associated with herpes zoster.

Kindly add the following new claims 8 and 9:

8. (New) A therapeutic agent for neuropathic pain according to Claim 2, wherein said neuropathic pain is pain associated with herpes zoster.

9. (New) A therapeutic agent for neuropathic pain according to Claim 3, wherein said neuropathic pain is pain associated with herpes zoster.

Remarks

We respectfully request that the above-identified amendments entered into the file of the case. They are made to correct typographical and grammatical errors and to remove multiple dependent claims. No new matter has been added.

An early action on the merits of the case is respectfully requested.

Respectfully submitted,

T. Daniel Christenbury
Reg. No. 31,750

TDC:gj
(215) 563-1810

Marked up Version with the Specification

Please replace the paragraph bridging between pages 18-20 with the following:

When the compounds represented by the general formula (I) are used as therapeutic agents for neuropathic pain, the compounds can be used alone or in combination with other compounds represented by the general formula (I) as active ingredients. After the compounds are purified and pass the necessary stability test, the compounds can be orally or parenterally administered as they are, or as pharmaceutical compositions mixed with know, pharmacologically acceptable acids, carrier, excipients, etc. Examples of administration modes include injections, orally administered drugs, such as tablets, capsules, granules, powdered drugs, and syrups, and administration per rectum by suppositories. The content of the active ingredient in the therapeutic agent for neuropathic pain of the present invention is preferably 1 to 90% by weight, and more preferably, 30 to 70% by weight. Although the dosage is appropriately selected depending on the symptoms, age, body weight, administration modes, etc., the dose per day for an adult is 0.0001 mg to 1 g in the case of injections, and 0.005 mg to 10 g in the case of orally administered drugs, and administration can be performed once or several times a day. Additionally, various adjuvants may be mixed therewith in order to improve the therapeutic effects on neuropathic pain. Furthermore, the therapeutic agents of the present invention may be combined with known drugs used for treating pain. Examples of drugs which can be combined with the therapeutic agent include, but are not particularly limited to, antidepressants, antianxiety agents, anticonvulsants, topical anesthetics, sympathetic agents, NMDA-receptor antagonists, calcium channel blockers, serotonin receptor antagonists, GABA-receptor activators, opioid agonists, and antiinflammatory agents. More specifically, the examples are amitriptyline, imipramine, desipramine, fluoxetine, carbamazepine, diazepam, gabepentin, valproic acid, ~~carbamazepine,~~ lidocaine, clonidine, phentolamine, prazosin, ketamine, ifenprodil,

dextromethorphan, mexiletine, ketanserin, sarpogrelate hydrochloride, benzodiazepine, barbiturate, tramadol, fentanyl, and dicrofenac. Furthermore, in the case of treatment for neuropathjc pain caused by virus infection, antiviral agents, such as aciclovir and famciclovir, can be combined with the therapeutic agent of the present invention. In addition, nerve block therapy, acupuncture, actinotherapy, epidural electro-stimulation therapy, etc. that are used for treatment of neuropathic pain can be combined with the therapeutic agent of the present invention.

Please replace the paragraph bridging between pages 22-23 with the following:

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methyl group; R^2 is hydrogen, a hydroxy group, an acetoxy group, or a methoxy group; R^3 is hydrogen, a hydroxy group, an acetoxy group, a methoxy group, or a benzyloxy group; X is CH; m is an integer from 0 to 2; an integer m of R^4 is independently fluoro, chloro, bromo, a methyl group, a methoxy group, a nitro group, or an amino group.

Marked up version in the Claims

4. (Amended) A therapeutic agent for neuropathic pain according to ~~any one of Claims 1 to 3~~Claim 1, wherein said neuropathic pain is pain associated with herpes zoster.

Kindly add the following new claims 8 and 9:

8. (New) A therapeutic agent for neuropathic pain according to Claim 2, wherein said neuropathic pain is pain associated with herpes zoster.

9. (New) A therapeutic agent for neuropathic pain according to Claim 3, wherein said neuropathic pain is pain associated with herpes zoster.

(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

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2001年3月1日 (01.03.2001)

PCT

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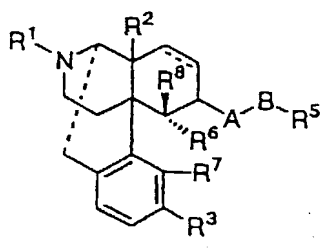
(81) 指定国 (国内): CA, CN, JP, US.

(84) 指定国 (広域): ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

添付公開書類:
— 国際調査報告書

(54) Title: REMEDIES FOR NEUROPATHIC PAIN AND MODEL ANIMALS OF NEUROPATHIC PAIN

(54) 発明の名称: 神経因性疼痛治療剤および神経因性疼痛のモデル動物



(I)

(57) Abstract: Remedies for neuropathic pain which contain as the active ingredient compounds represented by general formula (I) (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A and B are each as defined in the description) or pharmacologically acceptable salts thereof; and model animals prepared by administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline. These remedies and model animals enable drug therapy for neuropathic pain and, moreover, evaluation of the therapeutic effects of compounds on neuropathic pain.

WO 01/14383 A1

[続葉有]

8/Pats

DESCRIPTION

THERAPEUTIC AGENT FOR NEUROPATHIC PAIN AND NEUROPATHIC PAIN ANIMAL MODEL

Technical Field

The present invention relates to therapeutic agents for neuropathic pain containing opioid κ-receptor agonist compounds as active ingredients. The present invention also relates to a neuropathic pain animal model, a method for producing the model, a method for evaluating an effective compound for treating neuropathic pain using the model, and an effective compound for treating neuropathic pain which is obtained by the evaluation method.

Background Art

In neuropathic pain, which predominates in inveterate pain, even in the absence of stimuli to nociceptors due to tissue damage, persistent, unbearable, burning pain is caused, and in many cases, it may be complicated with paroxysmal pain. Additionally, hypoesthesia may occur in pain locations, and allodynia, in which pain is initiated by a slight stimulus which does not normally provoke pain, may often be observed. Clinically, these characteristic symptoms are mixed in the individual diseases. The International Association for the Study of Pain defines neuropathic pain as pain caused by a primary lesion or dysfunction of the nervous system, and the nervous system includes the peripheral nervous system and the central nervous system. Specifically, neuropathic pain can be related to peripheral nerve disorders (e.g.,

diabetes, alcoholic and other drug poisoning, and amyloidosis), amputation, posterior rhizotomy, brachial plexus avulsion injuries, spinal cord injuries, multiple sclerosis, the Parkinsonian syndrome, etc., and can be postherpetic neuralgia, central postapoplectic pain (so-called thalamic pain), etc. That is, neuropathic pain is caused by organic changes or dysfunction of the nervous system due to external injuries to the peripheral or central nervous system itself, infection, ischaemia, etc.

Morphine, which is widely used for treating pain, does not have a sufficient effect on the treatment of neuropathic pain, and also neuropathic pain is often resistant to opioid analgesics. Under the circumstances, development of effective therapeutic agents for inveterate pain including neuropathic pain has been desired. Examples of known therapeutic methods include surgical treatment, such as therapeutic spinal cord stimulation and dorsal root entry zone lesions, and chronic intrathecal administration of Baclofen, which is a γ-aminobutyric acid (GABA) receptor agonist, and ketamine, which is an N-methyl-D-aspartate (NMDA) receptor antagonist. However, since these methods are highly invasive, less invasive therapeutic methods have been desired, and thus it is important to develop new drugs effective against neuropathic pain.

On the other hand, although Japanese Patent No. 2525552 discloses morphinan derivatives having opioid κ-receptor agonist activity and analgesic action, the therapeutic effects of these compounds on neuropathic pain are not disclosed.

An animal model which shows the same clinical symptoms as those of human neuropathic pain is essential to the development of effective new drugs for neuropathic pain. Currently, with respect to the neuropathic pain animal model, although cutting and ligature of the peripheral nerve (G. J. Bennet & Y. K. Xie, Pain, 33: 87-107, 1988) or damage to the spinal cord (J. X. Hao, Pain, 45: 175-185, 1991) are conducted, complex operations must be performed for screening, and therefore, development of a simple animal model for neuropathic pain has been desired.

On the other hand, an intrathecal administration method using a rodent, particularly a mouse, is known as a method which can be performed relatively simply without anesthetization (J. L. K. Hylden & G. L. Wilcox, Eur. J. Pharmacol., 67: 313-316, 1980). It has also been reported that when NMDA (L. M. Aanonsen & G. L. Wilcox, J. Pharmacol. Exp. Ther., 243: 9-19, 1987) and substance P (J. L. K. Hylden & G. L. Wilcox, Brain Res., 217: 212-215, 1981) are intrathecally administered to mice, scratching, biting, and licking behavior, namely, SBL behavior, appears, suggesting the generation of pain. It has also been reported that by intrathecally administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline to mice, hyperalgesia is generated (L. F. Tseng et al., J. Pharmacol. Exp. Ther., 280: 600-605, 1997). However, these animal models are exhibited as drug-induced nociceptive reaction models, and their usefulness as neuropathic pain models is not disclosed.

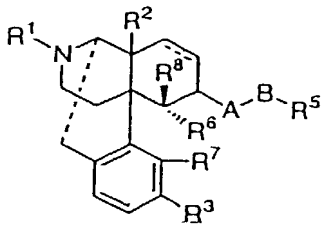
It is an object of the present invention to provide a therapeutic agent for neuropathic pain. It is another object of the present

invention to provide a neuropathic pain animal model in which the therapeutic effect of a drug against neuropathic pain can be evaluated, to provide a method for evaluating an effective compound for treating neuropathic pain using the animal model, and to provide a compound obtained by the evaluation method.

Disclosure of Invention

The present inventors have carried out thorough research to overcome the difficulties described above, and have discovered that a compound represented by general formula (I) alleviates neuropathic pain. It has also been discovered that an animal model which generates neuropathic pain can be produced by administering an octahydroisoquinoline derivative represented by general formula (II), and that the animal model can be used for the evaluation of a compound which alleviates neuropathic pain, and thus the present invention has been achieved.

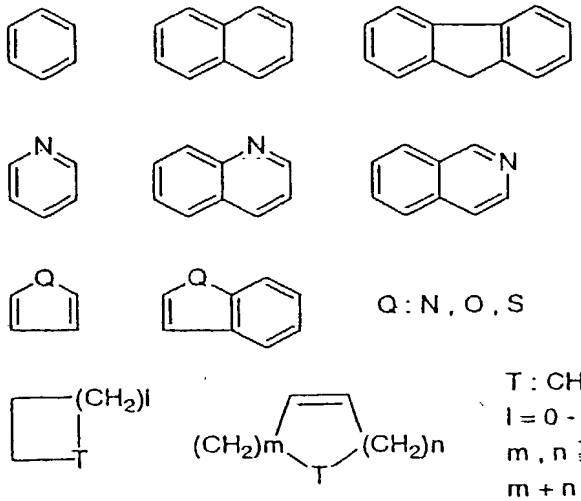
That is, in one aspect of the present invention, a therapeutic agent for neuropathic pain contains, as an active ingredient, a compound represented by general formula (I) or a pharmacologically acceptable acid addition salt thereof:



(I)

wherein ··· represents a double bond or a single bond; R^1 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aryl group having 6 to 12 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 represents hydrogen, a hydroxy group, a nitro group, an alkanoyloxy group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkyl group having 1 to 5 carbon atoms, or $-NR^9R^{10}$; R^9 represents hydrogen or an alkyl group having 1 to 5 carbon atoms; R^{10} represents hydrogen, an alkyl group having 1 to 5 carbon atoms, or $-C(=O)R^{11}$; R^{11} represents hydrogen, a phenyl group, or an alkyl group having 1 to 5 carbon atoms; R^3 represents hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; A represents $-XC(=Y)-$, $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where each of X, Y, and Z independently represents NR^4, S, or O; R^4 represents hydrogen, a straight or branched alkyl group having 1 to 5 carbon atoms, or an aryl group having 6 to 12 carbon atoms; and each R^4 may be identical or different); B represents a valence bond, a straight or branched alkylene group having 1 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro

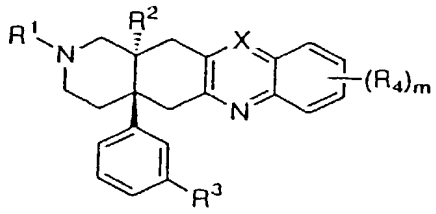
group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), a straight or branched acyclic unsaturated hydrocarbon containing one to three double bonds and/or triple bonds and having 2 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), or a straight or branched saturated or unsaturated hydrocarbon containing one to five thioether bonds, ether bonds, and/or amino bonds and having 1 to 14 carbon atoms (where any hetero atom is not directly bonded to A, and one to three methylene groups may be replaced with carbonyl groups); R^5 represents hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 represents hydrogen; R^7 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms, or R^6 and R^7 together forming -O-, $-CH_2-$, or -S-; and R^8 is hydrogen, an alkyl group having 1 to 5 carbon atoms, or an alkanoyl group having 1 to 5 carbon atoms.

In another aspect of the present invention, in a neuropathic pain animal model, pain reaction is generated by administering a compound represented by general formula (II):



(II)

wherein R^1 represents hydrogen, an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 3 to 7 carbon atoms,

a furan-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophene-2-yl-alkyl (where the alkyl moiety has 1 to 5 carbon atoms); R^2 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms; R^3 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, or an aralkyloxy group having 7 to 13 carbon atoms; X represents CH or N; m is an integer from 0 to 2; and each of integer m of R^4 is independently fluoro, chloro, bromo, iodo, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a nitro group, an amino group, or an alkylamino group. The present invention also relates to a method for evaluating a compound for alleviating neuropathic pain using the model, and to a compound obtained by the evaluation method.

Brief Description of the Drawings

Fig. 1 is a graph which illustrates that the pain-related behavior induced by intrathecal administration of Compound 1 increases dose-dependently.

Fig. 2 is a graph showing the effect of Baclofen, a $GABA_B$-receptor agonist, on the pain-related behavior induced by intrathecal administration of Compound 1.

Fig. 3 is a graph showing the effect of morphine on the pain-related behavior induced by intrathecal administration of Compound 1.

Fig. 4 is a graph showing the effect of Compound 2 on the pain-related behavior induced by intrathecal administration of Compound 1.

Fig. 5 is a graph showing the dose-dependent inhibitory action of Compound 2 on the pain-related behavior induced by intrathecal administration of Compound 1.

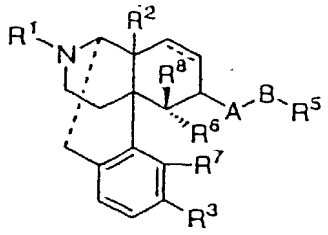
Fig. 6 is a graph showing the dose-dependent inhibitory action of Compound 2 when subcutaneously administered on the pain-related behavior induced by intrathecal administration of Compound 1.

Fig. 7 is a graph showing the action of Compound 2 in inhibiting allodynia and hyperalgesia in sciatic nerve ligation models.

Fig. 8 is a graph showing the action of Compound 2 in inhibiting allodynia and hyperalgesia in herpetic pain models.

Best Mode for Carrying Out the Invention

A therapeutic agent for neuropathic pain of the present invention contains, as an active ingredient, a compound represented by general formula (I) or a pharmacologically acceptable acid addition salt thereof:

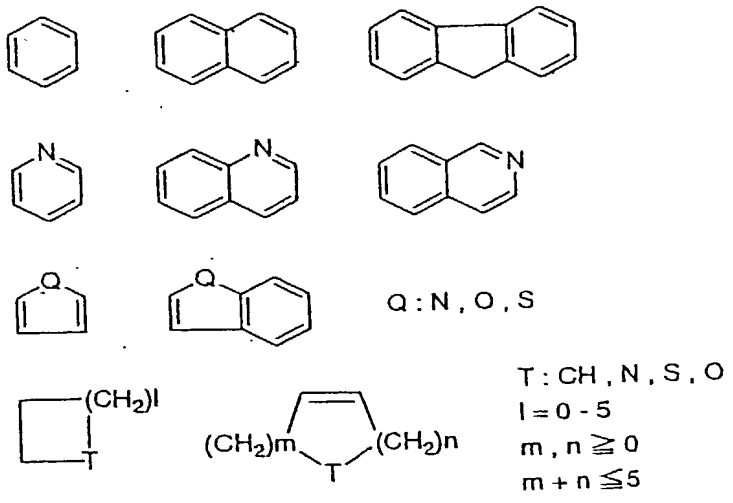


(I)

wherein ··· represents a double bond or a single bond; R^1 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4

to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aryl group having 6 to 12 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 represents hydrogen, a hydroxy group, a nitro group, an alkanoyloxy group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkyl group having 1 to 5 carbon atoms, or $-NR^9R^{10}$; R^9 represents hydrogen or an alkyl group having 1 to 5 carbon atoms; R^{10} represents hydrogen, an alkyl group having 1 to 5 carbon atoms, or $-C(=O)R^{11}$; R^{11} represents hydrogen, a phenyl group, or an alkyl group having 1 to 5 carbon atoms; R^3 represents hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; A represents $-XC(=Y)-$, $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where each of X, Y, and Z independently represents NR^4, S, or O; R^4 represents hydrogen, a straight or branched alkyl group having 1 to 5 carbon atoms, or an aryl group having 6 to 12 carbon atoms; and each R^4 may be identical or different); B represents a valence bond, a straight or branched alkylene group having 1 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), a straight or branched acyclic unsaturated hydrocarbon

containing one to three double bonds and/or triple bonds and having 2 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), or a straight or branched saturated or unsaturated hydrocarbon containing one to five thioether bonds, ether bonds, and/or amino bonds and having 1 to 14 carbon atoms (where any hetero atom is not directly bonded to A, and one to three methylene groups may be replaced with carbonyl groups); R^5 represents hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 represents hydrogen; R^7 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms, or R^6 and R^7 together forming -O-, $-CH_2-$, or -S-; and R^8 represents hydrogen, an alkyl group having 1 to 5 carbon atoms, or an alkanoyl group having 1 to 5 carbon atoms.

In the compound represented by general formula (I), preferable examples of R^1 include an alkyl group having 1 to 5 carbon atoms, a cycloalkylmethyl group having 4 to 7 carbon atoms, a cycloalkenylmethyl group having 5 to 7 carbon atoms, a phenylalkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, and a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms, and more preferable examples of R^1 include methyl, ethyl, propyl, butyl, isobutyl, cyclopropylmethyl, allyl, benzyl, phenethyl, furan-2-yl-methyl, and thiophene-2-yl-methyl groups.

Preferable examples of R^2 include hydrogen and hydroxy, nitro, acetoxy, methoxy, methyl, ethyl, propyl, amino, dimethylamino,

acetylamino, and benzoylamino groups, and more preferable examples of R^2 include hydrogen and hydroxy, nitro, acetoxy, methyl, and dimethylamino groups.

Preferable examples of R^3 include hydrogen and hydroxy, acetoxy, and methoxy groups, and more preferable examples of R^3 include hydroxy, acetoxy, and methoxy groups.

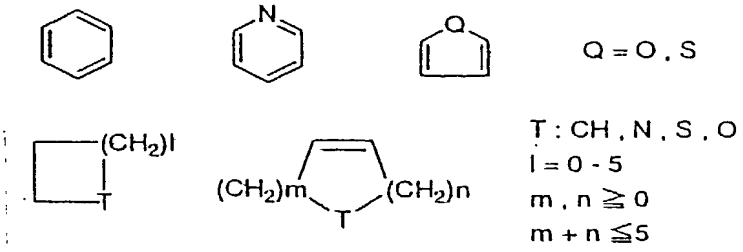
Preferable examples of A include $-NR^4C(=O)-$, $-NR^4C(=S)-$, $-NR^4C(=O)O-$, $-NR^4C(=O)NR^4-$, $-NR^4C(=S)NR^4-$, $-NR^4C(=O)S-$, $-OC(=O)-$, $-OC(=O)O-$, $-SC(=O)-$, $-NR^4-$, $-O-$, $-NR^4SO_2-$, and OSO_2-, and more preferable examples of A include $-NR^4C(=O)-$, $-NR^4C(=S)-$, $-NR^4C(=O)O-$, $-NR^4C(=O)NR^4-$, $-NR^4C(=S)NR^4-$, and $-NR^4SO_2-$.

Preferable examples of R^4 include hydrogen and straight or branched alkyl groups having 1 to 5 carbon atoms, and more preferable examples of R^4 include a straight or branched alkyl group having 1 to 5 carbon atoms, and particularly, methyl, ethyl, propyl, butyl, and isobutyl groups. Among them, $-XC(=Y)-$ (where X represents NR^4, S, or O; Y represents O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms), $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where X represents NR^4; Y represents O or S; Z represents NR^4 or O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms) is preferred, and $-XC(=Y)-$ or $-XC(=Y)Z-$ (where X represents NR^4; Y represents O; and R^4 represents an alkyl group having 1 to 5 carbon atoms) is more preferred.

Preferable examples of B include $-(CH_2)_n-$ (n = 0 to 10), $-(CH_2)_n-C(=O)-$ (n = 1 to 4), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, $-CH_2-S-$, $-(CH_2)_2-O-CH_2-$, and $-CH=CH-CH=CH-(CH_2)_n-$ (n = 0 to

4), and more preferable examples of B include $-(CH_2)_n-$ (n = 1 to 3), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, and $-CH_2-S-$. Among them, a linear alkylene group having 1 to 6 carbon atoms, $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-CH=CH-$, $-C\equiv C-$, $-CH_2-O-$, or $-CH_2-S-$ is most preferable. Particularly, $-CH=CH-$ or $-C\equiv C-$ is desirable. (Of course, the preferable examples include the groups which have various substituents described above.)

Preferable examples of R^5 include hydrogen and organic groups having the following basic skeletons:



ORGANIC GROUPS REPRESENTED BY R^5

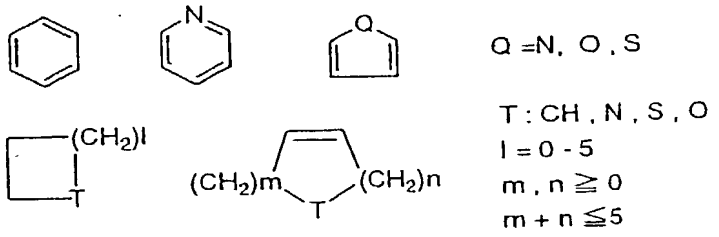
(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group). Among them, more preferred are hydrogen and organic groups having the following basic skeletons:

ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group). More specifically, preferable examples include, but are not limited to, hydrogen and phenyl, 4-methylphenyl, 3-methylphenyl, 2-methylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 3,4-dimethoxyphenyl, 4-hydroxyphenyl, 3-hydroxyphenyl, 3,4-dihydroxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 3,4-difluorophenyl, perfluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 2,4,5-trichlorophenyl, 2,4,6-trichlorophenyl, 4-bromophenyl, 3-bromophenyl, 2-bromophenyl, 4-nitrophenyl, 3-nitrophenyl, 2-nitrophenyl, 4-aminophenyl, 3-aminophenyl, 2-aminophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 3,4-methylenedioxyphenyl, 3-furanyl, 2-furanyl, 3-thienyl, 2-thienyl, cyclopentyl, and cyclohexyl groups.

In the compound represented by general formula (I), preferably, R^1 is an alkyl group having 1 to 5 carbon atoms, a cycloalkylmethyl group

having 4 to 7 carbon atoms, a cycloalkenylmethyl group having 5 to 7 carbon atoms, a phenylalkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 is hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; R^3 is hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; A is $-XC(=Y)-$ (where X represents NR^4, S, or O; Y represents O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms), $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where X represents NR^4; Y represents O or S; Z represents NR^4 or O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms); B is $-(CH_2)_n-$ (n = 0 to 10), $-(CH_2)_n-C(=O)-$ (n = 1 to 4), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, $-CH_2-S-$, $-(CH_2)_2-O-CH_2-$, or $-CH=CH-CH=CH-(CH_2)_n-$ (n = 0 to 4); R^5 is hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from

the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 and R^7 together form -O-; and R^8 is hydrogen.

In the compound represented by general formula (I), more preferably, R^1 is a methyl, ethyl, propyl, butyl, isobutyl, cyclopropylmethyl, allyl, benzyl, phenethyl, furan-2-yl-methyl, or thiophene-2-yl-methyl group; R^2 is hydrogen, a hydroxy group, or an acetoxy group; R^3 is a hydroxy, acetoxy, or methoxy group; A is $-XC(=Y)-$ or $-XC(=Y)Z-$ (where X represents NR^4; Y represents O; and R^4 represents an alkyl group having 1 to 5 carbon atoms); B is $-(CH_2)_n-$ (n = 1 to 3), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, or $-CH_2-S-$; R^5 is hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:

ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a

trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 and R^7 together form -O-; and R^8 is hydrogen.

The morphinan derivatives represented by general formula (I) may be produced by the method disclosed in Japanese Patent No. 2525552.

Preferable examples of pharmacologically acceptable acid addition salts include, but are not limited to, inorganic salts such as hydrochlorides, sulfates, nitrates, hydrobromides, hydroiodides, and phosphates; organic carboxylates such as acetates, lactates, citrates, oxalates, glutarates, malates, tartrates, fumarates, mandelates, maleates, benzoates, and phtalates; and organic sulfonates such as methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, and camphorsulfonates. More preferable examples include hydrochlorides, hydrobromides, phosphates, tartrates, maleates, and methanesulfonates.

Since the compounds represented by the general formula (I) or the pharmacologically acceptable salts thereof alleviate neuropathic pain in which sufficient therapeutic effects are not achieved by morphine, which is widely used as an analgesic, it has become clear that they are effective as therapeutic agents for neuropathic pain.

When the compounds represented by the general formula (I) are used as therapeutic agents for neuropathic pain, the compounds can be used alone or in combination with other compounds represented by the general formula (I) as active ingredients. After the compounds are purified and pass the necessary stability test, the compounds can be orally or parenterally administered as they are, or as pharmaceutical compositions

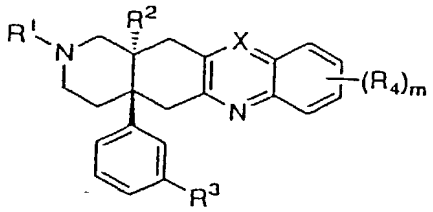
mixed with known, pharmacologically acceptable acids, carriers, excipients, etc. Examples of administration modes include injections, orally administered drugs, such as tablets, capsules, granules, powdered drugs, and syrups, and administration per rectum by suppositories. The content of the active ingredient in the therapeutic agent for neuropathic pain of the present invention is preferably 1 to 90% by weight, and more preferably, 30 to 70% by weight. Although the dosage is appropriately selected depending on the symptoms, age, body weight, administration modes, etc., the dose per day for an adult is 0.0001 mg to 1 g in the case of injections, and 0.005 mg to 10 g in the case of orally administered drugs, and administration can be performed once or several times a day. Additionally, various adjuvants may be mixed therewith in order to improve the therapeutic effects on neuropathic pain. Furthermore, the therapeutic agents of the present invention may be combined with known drugs used for treating pain. Examples of drugs which can be combined with the therapeutic agent include, but are not particularly limited to, antidepressants, antianxiety agents, anticonvulsants, topical anesthetics, sympathetic agents, NMDA-receptor antagonists, calcium channel blockers, serotonin receptor antagonists, GABA-receptor activators, opioid agonists, and antiinflammatory agents. More specifically, the examples are amitriptyline, imipramine, desipramine, fluoxetine, carbamazepine, diazepam, gabapentin, valproic acid, carbamazepine, lidocaine, clonidine, phentolamine, prazosin, ketamine, ifenprodil, dextromethorphan, mexiletine, ketanserin, sarpogrelate hydrochloride, benzodiazepine, barbiturate, tramadol,

fentanyl, and dicrofenac. Furthermore, in the case of treatment for neuropathic pain caused by virus infection, antiviral agents, such as aciclovir and famciclovir, can be combined with the therapeutic agent of the present invention. In addition, nerve block therapy, acupuncture, actinotherapy, epidural electro-stimulation therapy, etc. that are used for treatment of neuropathic pain can be combined with the therapeutic agent of the present invention.

From the viewpoint of the causes of pain, neuropathic pain to be treated includes pain developing when damage and dysfunction occur in the nervous system itself due to external injuries, surgery, radiation therapy or drug therapy, and also due to diabetes, alcoholic and other drug poisoning, amyloidosis, virus infection, etc., without stimuli to nociceptors due to tissue damage. From the viewpoint of the locations of the nerves in which dysfunction occurs, examples of neuropathic pain include trigeminal neuralgia, glossopharyngeal neuralgia, causalgia (a pain syndrome in which vascular nerve disorders and dyshidrosis occur due to sympathetic nerve dysfunction where there has been partial damage to the peripheral nerves of limbs or the large branches thereof, and persistent, burning pain and nutritional disorders of tissues are observed), reflex sympathetic dystrophy, deafferentation pain, and thalamic pain. Other examples are herpetic pain, postherpetic neuralgia, tonic spasm pain, erythermalgia, poliomyelitis pain, phantom limb pain, pain in AIDS-infected patients, multiple sclerosis pain, and pain associated with the Parkinsonian syndrome. In particular, the therapeutic agent of the present invention is effective in treating pain

associated with zosteriform skin lesions, for example, herpetic pain and postherpetic neuralgia.

The present invention also relates to an animal model in which pain reaction is generated by administering a compound represented by general formula (II) to the animal, to a method for evaluating a compound for alleviating neuropathic pain using the model, and to a compound obtained by the evaluation method:



(II)

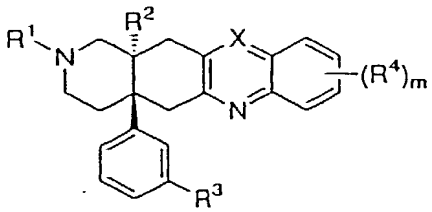
wherein R^1 represents hydrogen, an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 3 to 7 carbon atoms, a furan-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophene-2-yl-alkyl (where the alkyl moiety has 1 to 5 carbon atoms); R^2 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms; R^3 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, or an aralkyloxy group having 7 to 13 carbon atoms; X represents CH or N; m is an integer from 0 to 2; and each of integer m of R^4 is independently fluoro, chloro, bromo, iodo, an alkyl group having 1 to 5 carbon atoms,

an alkoxy group having 1 to 5 carbon atoms, a nitro group, an amino group, or an alkylamino group.

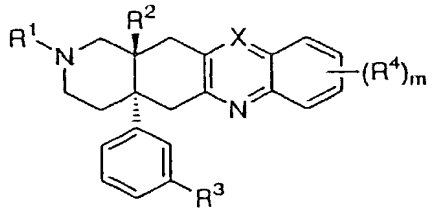
In the compound, which is used for making the animal model, represented by general formula (II), preferably, R^1 is hydrogen, an alkyl group having 1 to 5 carbon atoms, a cycloalkylmethyl group having 4 to 7 carbon atoms, a cycloalkenylmethyl group having 5 to 7 carbon atoms, a phenyl group, a naphthyl group, a phenylaralkyl group having 7 to 13 carbon atoms, an alkenyl group having 3 to 7 carbon atoms, a furan-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophene-2-yl-alkyl group (where the alkyl moiety has 1 to 5 carbon atoms); R^2 is hydrogen, a hydroxy group, an acetoxy group, a propionoxy group, a methoxy group, or an ethoxy group; R^3 is hydrogen, a hydroxy group, an acetoxy group, a propionoxy group, a methoxy group, and ethoxy group, or a benzyloxy group; X is CH; m is an integer from 0 to 2; and R^4 is independently fluoro, chloro, bromo, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a nitro group, or an amino group. More preferably, R^1 is hydrogen, a methyl group, an ethyl group, a cyclopropylmethyl group, a cyclobutylmethyl group, a cyclopentylmethyl group, a cyclopentenylmethyl group, a cyclohexenylmethyl group, a benzyl group, a phenethyl group, a trans-2-butenyl group, a 3-methyl-2-butenyl group, an allyl group, a furan-2-yl-methyl group, or a thiophene-2-yl-methyl group; R^2 is hydrogen, a hydroxy group, an acetoxy group, or a methoxy group; R^3 is hydrogen, a hydroxy group, an acetoxy group, a methoxy group, or a benzyloxy group; X is CH; m is an integer from 0 to 2; and integer m of

R^4 is independently fluoro, chloro, bromo, a methyl group, a methoxy group, a nitro group, or an amino group.

General formula (II) shows a relative configuration of the compound, and examples of the compound of the present invention include racemic modifications, and optical isomers of which absolute structures are represented by general formulae (A) and (B) below. The optical isomers of which structures are represented by general formula (A) are preferable.

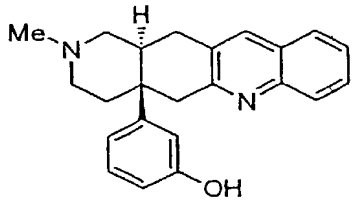


(A)



(B)

More preferable is (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octohydro-trans-quinolino[2,3-g]isoquinoline of which the formula is shown below.



The animal used in the present invention is not particularly limited, but is preferably a rodent and more preferably a mouse. The compound to generate neuropathic pain is preferably administered intrathecally. When a mouse is used, although the strain, age in weeks,

sex, etc., of the mouse are not particularly limited, as the age in weeks increases, that is, as the body weight increases, intrathecal administration to the animal becomes more difficult. Therefore, a mouse with a body weight of 25 to 35 g is preferably used.

In order to induce neuropathic pain in a mouse, desirably, the compound represented by general formula (II) is intrathecally administered in an amount of approximately 5 to 30 μg, and usually, approximately 15 μg is preferably used. As the solvent for administration, an isotonic solution is preferably used, and an ordinary physiological saline solution can be used sufficiently. The intrathecal dosage is preferably in the range of several to 20 μl, and more preferably approximately 5 μl. When intrathecal administration is performed, an injection needle of 25 to 30 gauges is preferably used.

In the evaluation method of the present invention, various types of indexes for animal behavioral response can be used. Preferably, scratching, biting, and licking behavior and the like which are not often observed in normal animals are used as indexes. In order to make evaluations by observing such behavior, the animals may be directly observed. Alternatively, evaluations may be made using recording media such as videos, or using machines which detect the movements of animals based on heat emitted by the animals, or the like. With respect to the evaluation time, the period in which the behavior is stably developed after the administration of the compound represented by general formula (II) is desirable, and in particular, evaluation is preferably made for 5 minutes from 5 minutes after administration.

When screening or evaluation of a drug for treating neuropathic pain is made using the animal model of the present invention, the administration route of the drug to be evaluated, solvent, dosage, etc., are not particularly limited, and they can be appropriately selected in consideration of the characteristics of the drug itself.

By the evaluation method described above, a compound which inhibits the behavior of the animal, for example, scratching, biting, and licking, can be obtained as a compound which alleviates neuropathic pain.

Since the compound thus obtained demonstrates effectiveness in other neuropathic pain animal models, the animal model is proved to be useful. Accordingly, it is possible to evaluate a compound, and a compound which demonstrates effectiveness can be developed as a therapeutic agent for neuropathic pain. Therefore, the animal model, the evaluation method using the animal model, screening or evaluation of the drug, and the compound obtained by the evaluation described above lead to great progress in the development of drugs for treating neuropathic pain.

The present invention will be described in detail based on the examples below.

[Examples]

Example 1: Production of the Neuropathic Pain Animal Model

Mice (ddY; weighing 22 to 25 g when the experiment was started) were kept in a plastic cage at a constant temperature and humidity (22 ± 1°C, 55 ± 5%) under a 12-hour light-dark cycle. The mice had free

access to food and water.

(+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline (Compound 1) was dissolved in a physiological saline solution (Ohtsuka Pharmaceutical Co., Ltd.) and was intrathecally administered to the mice without anesthetization. The intrathecal dose of the drug solution per mouse was 4 μl, and a 30 gauge needle and a 25 μl Hamilton syringe were used according to the method disclosed by Hylden and Wilcox (J. L. K. Hylden & G. L. Wilcox, Eur. J. Pharmacol., 67: 313-316, 1980).

Scratching, biting, and licking behavior was regarded as an index of tentative responses for nociception, and the duration of such behavior was measured for 5 minutes from 5 minutes after the administration of Compound 1 in a transparent acrylic cage (20 × 13 × 10 cm) in a single-blind manner. The results thereof are shown in Fig. 1. When Compound 1 was administered in an amount of 7.5 μg/mouse or more, the tentative responses for nociception increased significantly and dose-dependently. As shown in Fig. 2, the tentative responses for nociception induced by 15 μg/mouse of Compound 1 were inhibited dose-dependently by simultaneous intrathecal administration of Baclofen, a $GABA_B$-receptor agonist. However, as shown in Fig. 3, when morphine was intrathecally administered to mice simultaneously with compound 1, the tentative responses for nociception induced by 15 μg/mouse of Compound 1 were not inhibited at all.

Baclofen is currently clinically used as a therapeutic agent for convulsion/paralysis due to cerebral vascular disorders and multiple

sclerosis, and in animal experiments, it is known that an antinociceptive action is produced by systemic administration, intraventricular administration, and intrathecal administration. Furthermore, neuropathic pain is inhibited by the intrathecal administration of Baclofen, and the application thereof as a therapeutic agent for neuropathic pain is expected clinically. Morphine does not demonstrate effectiveness against neuropathic pain clinically. Consequently, it has become clear that the animal model of the present invention produced by intrathecally administering Compound 1 has characteristics of neuropathic pain.

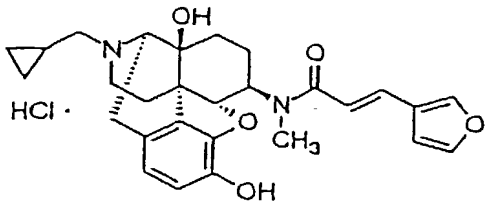
Example 2: Evaluation of the Action of Inhibiting Neuropathic Pain - 1

Mice (ddY; weighing 22 to 25 g when the experiment was started) were kept in a plastic cage at a constant temperature and humidity (22 ± 1°C, 55 ± 5%) under a 12-hour light-dark cycle. The mice had free access to food and water.

Compound 1 was dissolved in a physiological saline solution (Ohtsuka Pharmaceutical Co., Ltd.) and was intrathecally administered to the mice without anesthetization. The intrathecal dose of the drug solution per mouse was 4 μl, and a 30 gauge needle and a 25 μl Hamilton syringe were used according to the method disclosed by Hylden and Wilcox (J. L. K. Hylden & G. L. Wilcox, Eur. J. Pharmacol., 67: 313-316, 1980).

(-)-17cyclopropyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-trans-3-(3-furyl)acrylamide]morphinan hydrochloride (Compound 2) (H. Nagase et

al. Chem. Pharm. Bull. 46, 366, 1998), of which the formula is shown below,



2

as a selective opioid κ-receptor agonist compound, was intrathecally administered to the mice simultaneously with Compound 1, and the effect thereof on neuropathic pain was evaluated based on tentative responses for nociception, such as scratching, biting, and licking behavior, as indexes. The duration of such behavior was measured for 5 minutes from 5 minutes after the administration of the simultaneous administration of Compound 2 and Compound 1 (15 μg/mouse) in a transparent acrylic cage (20 × 13 × 10 cm) in a single-blind manner. Additionally, Compound 2 was dissolved in a physiological saline solution for use. The results thereof are shown in Fig. 4. As is obvious from the graph, Compound 2 at 10 nmol/mouse significantly inhibited the tentative responses for nociception compared to the physiological saline solution-treated group, thus exhibiting effectiveness for treating neuropathic pain.

Example 3: Evaluation of the Action of Inhibiting Neuropathic Pain - 2

In order to determine the effect of the drug on neuropathic pain, tentative responses for nociception were tested in the case in which a

low dose of 1 or 3 nmol/mouse of Compound 2 was intrathecally administered simultaneously with Compound 1 in a manner similar to that of Example 2 and in the case in which Compound 2 was subcutaneously administered so that systemic exposure to the drug was evaluated. The results thereof are shown in Figs. 5 and 6. In either case, it was demonstrated that the tentative responses for nociception are dose-dependently inhibited and Compound 2 is effective against neuropathic pain. Since the effectiveness of Compound 2 has also been shown in systemic exposure, it has become clear that Compound 2 is effective even if the drug is not administered topically, that is, even if the drug is administered in various dosage forms which are pharmacologically acceptable.

Example 4: Evaluation of the Action of the Drug in Inhibiting Neuropathic Pain in a Sciatic Nerve Ligation Model

The action of Compound 2 in inhibiting neuropathic pain was investigated using another, widely known neuropathic pain model. That is, the action of Compound 2 in a sciatic nerve ligation mouse model was investigated using a method in which the method disclosed by A. B. Malmberg and A. I. Basbaum (Pain, 76, 215-222, 1998) et al. was slightly modified. In order to measure allodynia or hyperalgesia generally observed in neuropathic pain, two von Frey hairs (0.17 and 1.48 g) having different strengths were used. Four weeks following the surgery, the mice were placed in an acrylic cage (90 x 100 x 300 mm) and allowed to acclimate for a minimum of 30 minutes. The von Frey hairs were

applied perpendicularly to the soles of the hind feet so as to cause slight bending for a duration of approximately 3 seconds. This was repeated 6 times at intervals of several seconds. The reaction of the mouse was given a score in the manner described below.

0: No reaction

1: Lifting of hind foot

2: Immediate escape reaction and flinching of hind paw

The reactions of the surgically operated foot and the opposite foot as control were measured before the administration of the drug, and 30 minutes and 2 hours after the administration of the drug. The difference between the score of the surgically operated foot and the score of the control foot was evaluated as allodynia or hyperalgesia. That is, the larger difference indicates the larger degree of allodynia or hyperalgesia. Compound 2 was dissolved in a physiological saline solution and the drug solution was subcutaneously administered. Additionally, a physiological saline solution was used as a control solvent. The results thereof are shown in Fig. 7. Before the administration of the drug, in both groups, allodynia or hyperalgesia symptoms were shown and each difference between the score of the surgically operated foot and the score of the control foot was same. Thirty minutes after the administration, Compound 2 inhibited allodynia or hyperalgesia while the control-solvent-administered group did not show the improvement effect. After 2 hours, the effect of the drug disappeared. From the results described above, it was found that the compound which showed effectiveness in the neuropathic pain model in

Example 1 also shows effectiveness in another neuropathic pain model.

Example 5: Evaluation of the Action of the Drug in Inhibiting Hyperalgesia and Allodynia in Pain Associated with zosteriform skin lesions

The therapeutic effect of Compound 2 on pain associated with zoster classified under neuropathic pain was investigated. The evaluation of the therapeutic effect was made using an animal model produced according to a method disclosed in Pain, 86, 95-101, 2000. The results when Compound 2 was orally administered are shown in Fig. 8. Thirty minutes after the administration, Compound 2 dose-dependently inhibited allodynia or hyperalgesia associated with zosteriform skin lesions, and thus it was found that Compound 2 shows effectiveness against pain associated with zoster.

The examples described above have proved that when a compound is evaluated using the animal model in Example 1, a compound which shows effectiveness has an effect of improving allodynia or hyperalgesia in another neuropathic pain animal model. Consequently, it has been confirmed that the animal model in Example 1 and the evaluation method of a compound using the model are effective, and it has also become possible to develop a compound which shows effectiveness as a therapeutic agent for neuropathic pain. Therefore, it is believed that the animal model, the evaluation method using the animal model, screening or evaluation of the drug, and the compound obtained by the evaluation described above will lead to great progress in the

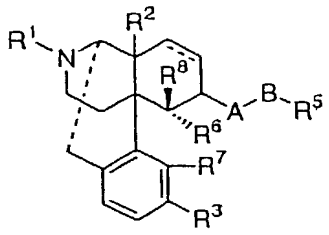
development of drugs for treating neuropathic pain.

Industrial Applicability

The therapeutic agent for neuropathic pain in the present invention is useful for drug treatment for neuropathic pain. The neuropathic pain animal model of the present invention is a simple model which shows similar symptoms to those of human neuropathic pain, and by using the animal model of the present invention, the therapeutic effect of the drug against neuropathic pain can be determined efficiently. That is, the present invention can greatly advance the development of drugs for treating neuropathic pain.

CLAIMS

1. A therapeutic agent for neuropathic pain comprising, as an active ingredient, a compound represented by general formula (I) or a pharmacologically acceptable acid addition salt thereof:

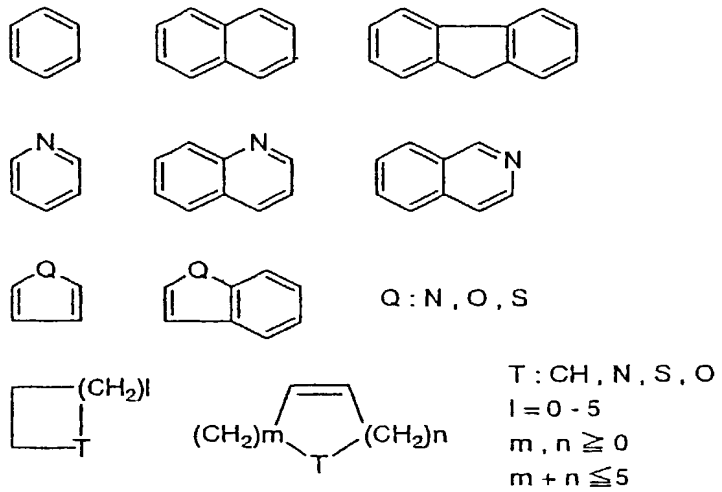


(I)

wherein ··· represents a double bond or a single bond; R^1 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aryl group having 6 to 12 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 represents hydrogen, a hydroxy group, a nitro group, an alkanoyloxy group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkyl group having 1 to 5 carbon atoms, or $-NR^9R^{10}$; R^9 represents hydrogen or an alkyl group having 1 to 5 carbon atoms; R^{10} represents hydrogen, an alkyl group having 1 to 5 carbon atoms, or $-C(=O)R^{11}$; R^{11} represents hydrogen, a phenyl group, or an alkyl group having 1 to 5 carbon atoms;

R^3 represents hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; A represents $-XC(=Y)-$, $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where each of X, Y, and Z independently represents NR^4, S, or O; R^4 represents hydrogen, a straight or branched alkyl group having 1 to 5 carbon atoms, or an aryl group having 6 to 12 carbon atoms; and each R^4 may be identical or different); B represents a valence bond, a straight or branched alkylene group having 1 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), a straight or branched acyclic unsaturated hydrocarbon containing one to three double bonds and/or triple bonds and having 2 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), or a straight or branched saturated or unsaturated hydrocarbon containing one to five thioether bonds, ether bonds, and/or amino bonds and having 1 to 14 carbon atoms (where any hetero atom is not directly bonded to A, and one to three methylene groups may be replaced with carbonyl groups); R^5 represents

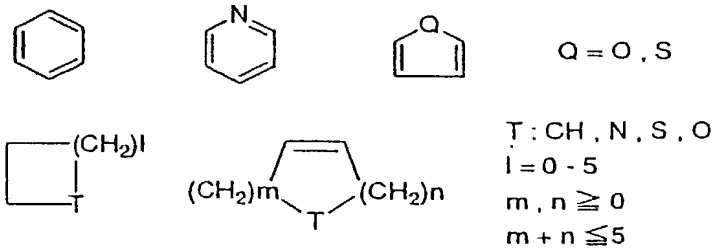
hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 represents hydrogen; R^7 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms, or R^6 and R^7 together forming $-O-$, $-CH_2-$, or $-S-$; and R^8 is hydrogen, an alkyl group having 1 to 5 carbon atoms, or an alkanoyl group having 1 to 5 carbon atoms.

2. A therapeutic agent for neuropathic pain according to Claim 1, wherein, in general formula (I), R^1 is an alkyl group having 1 to 5 carbon atoms, a cycloalkylmethyl group having 4 to 7 carbon atoms, a cycloalkenylmethyl group having 5 to 7 carbon atoms, a phenylalkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 is hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; R^3 has the same definition as Claim 1; A is $-XC(=Y)-$ (where X represents NR^4, S, or O; Y represents O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms), $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where X represents NR^4; Y represents O or S; Z represents NR^4 or O; and R^4 represents hydrogen or an alkyl group having 1 to 5 carbon atoms); B is $-(CH_2)_n-$ (n = 0 to 10), $-(CH_2)_n-C(=O)-$ (n = 1 to 4), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, $-CH_2-S-$, $-(CH_2)_2-O-CH_2-$, or $-CH=CH-CH=CH-(CH_2)_n-$ (n = 0 to 4); R^5 is hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 and R^7 together form -O-; and R^8 is hydrogen.

3. A therapeutic agent for neuropathic pain according to Claim 1, wherein, in general formula (I), R^1 is a methyl, ethyl, propyl, butyl, isobutyl, cyclopropylmethyl, allyl, benzyl, phenethyl, furan-2-yl-methyl, or thiophene-2-yl-methyl group; R^2 is hydrogen, a hydroxy group, or an acetoxy group; R^3 is a hydroxy, acetoxy, or methoxy group; A is -XC(=Y)- or -XC(=Y)Z- (where X represents NR^4; Y represents O; Z represents NR^4 or O, and R^4 represents an alkyl group having 1 to 5 carbon atoms); B is $-(CH_2)_n-$ (n = 1 to 3), $-CH=CH-(CH_2)_n-$ (n = 0 to 4), $-C\equiv C-(CH_2)_n-$ (n = 0 to 4), $-CH_2-O-$, or $-CH_2-S-$; R^5 is hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:

Q : O,S

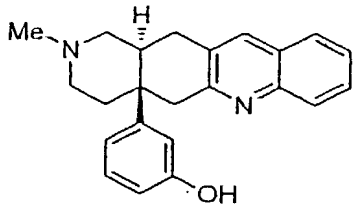
ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an

alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 and R^7 together form -O-; and R^8 is hydrogen.

4. A therapeutic agent for neuropathic pain according to any one of Claims 1 to 3, wherein said neuropathic pain is pain associated with herpes zoster.

5. A neuropathic pain animal model in which pain reaction is generated by intrathecally administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline



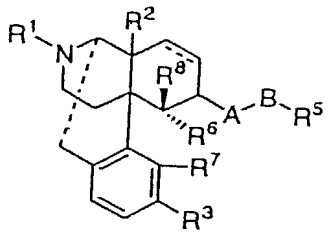
to a mouse.

6. A method for evaluating a compound for alleviating neuropathic pain in which a neuropathic pain animal model according to Claim 5 is used.

7. A compound obtained by an evaluation method according to Claim 6.

ABSTRACT

The present invention relates to a therapeutic agent for neuropathic pain containing, as an active ingredient, a compound represented by general formula (I) or a pharmacologically acceptable acid addition salt thereof:



(I)

(wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, and B have the same definitions as those described in the specification), and an animal model produced by administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octohydro-trans-quinolino[2,3-g]isoquinoline. The present invention makes it possible to perform drug treatment for neuropathic pain. The therapeutic effect of a compound against neuropathic pain can also be evaluated.

Fig. 1

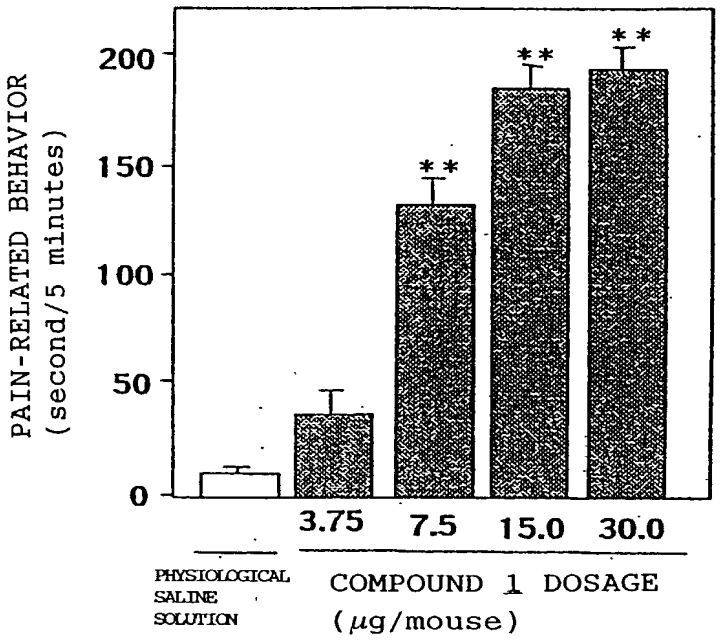


Fig. 2

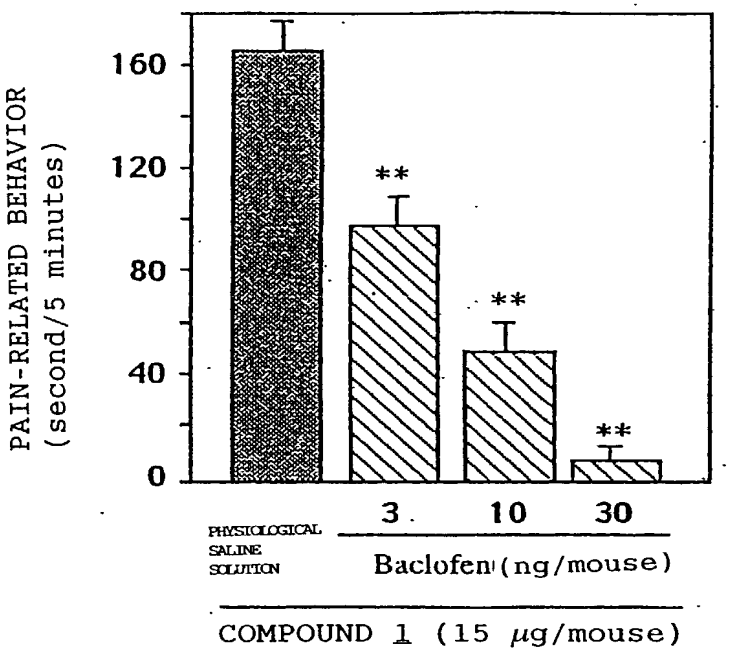

PAIN-RELATED BEHAVIOR
(second/5 minutes)
160
120
80
40
0
**
**
**
PHYSIOLOGICAL SALINE SOLUTION
3
10
30
Baclofen (ng/mouse)
COMPOUND 1 (15 μg/mouse)

Fig. 3

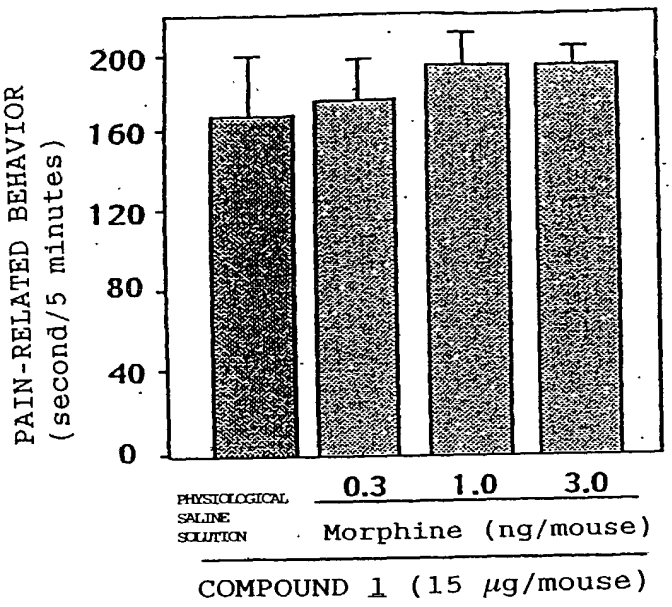

PAIN-RELATED BEHAVIOR
(second/5 minutes)
200
160
120
80
40
0
PHYSIOLOGICAL SALINE SOLUTION
0.3
1.0
3.0
Morphine (ng/mouse)
COMPOUND 1 (15 μg/mouse)

Fig. 4

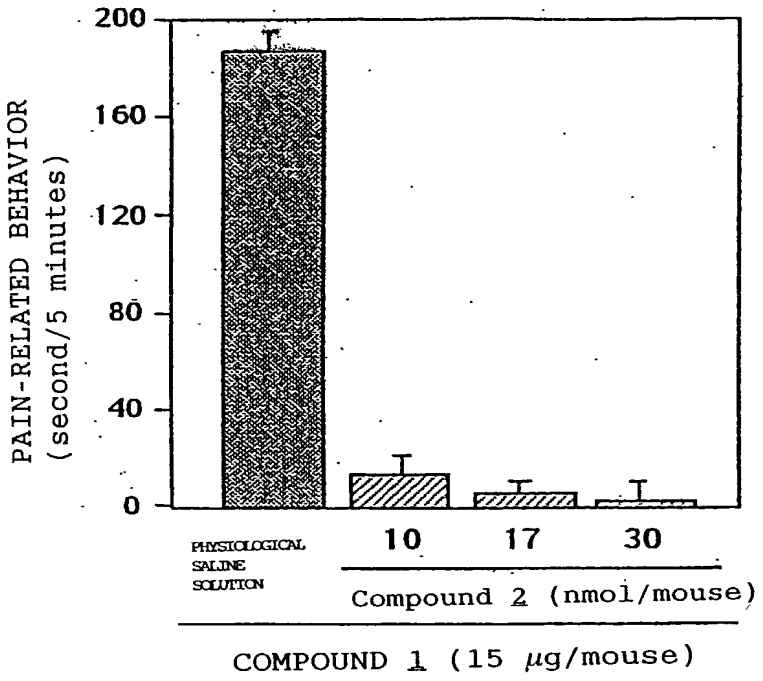

200
160
120
80
40
0
PAIN-RELATED BEHAVIOR
(second/5 minutes)
PHYSIOLOGICAL SALINE SOLUTION
10
17
30
Compound 2 (nmol/mouse)
COMPOUND 1 (15 μg/mouse)

Fig. 5

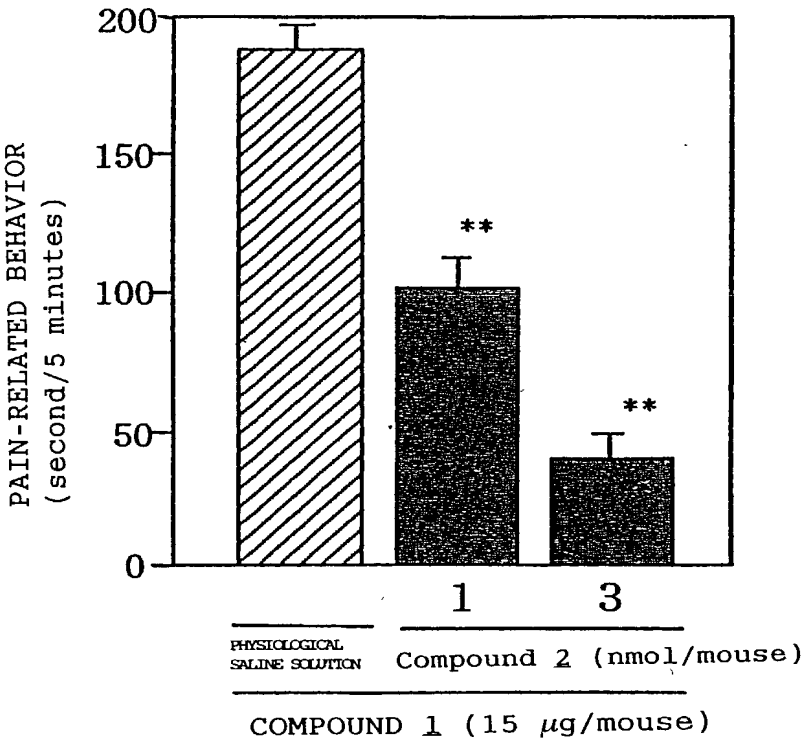

200
150
100
50
0
PAIN-RELATED BEHAVIOR
(second/5 minutes)
**
**
1
3
PHYSIOLOGICAL SALINE SOLUTION
Compound 2 (nmol/mouse)
COMPOUND 1 (15 μg/mouse)

Fig. 6

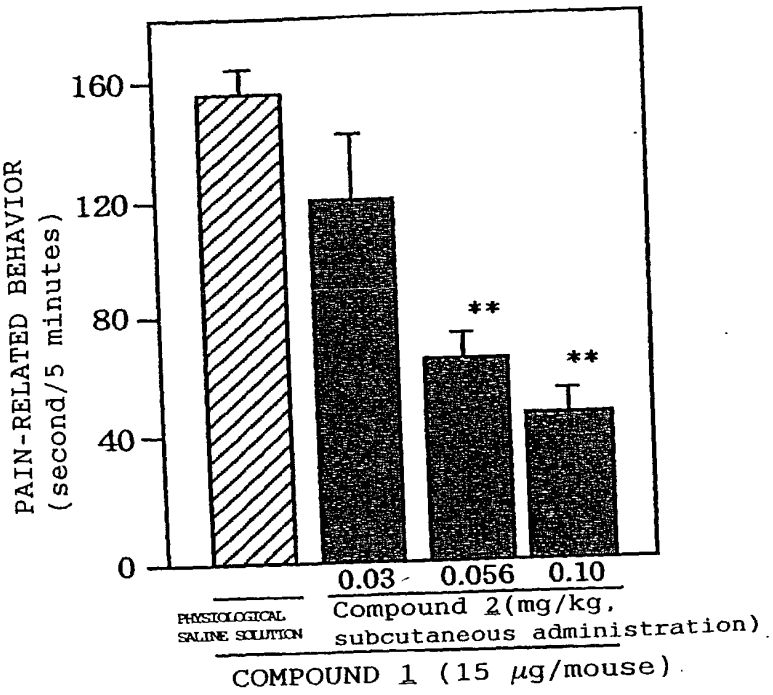

160
120
80
40
0
PAIN-RELATED BEHAVIOR
(second/5 minutes)
**
**
0.03
0.056
0.10
PHYSIOLOGICAL SALINE SOLUTION
Compound 2(mg/kg, subcutaneous administration)
COMPOUND 1 (15 μg/mouse)

Fig. 7

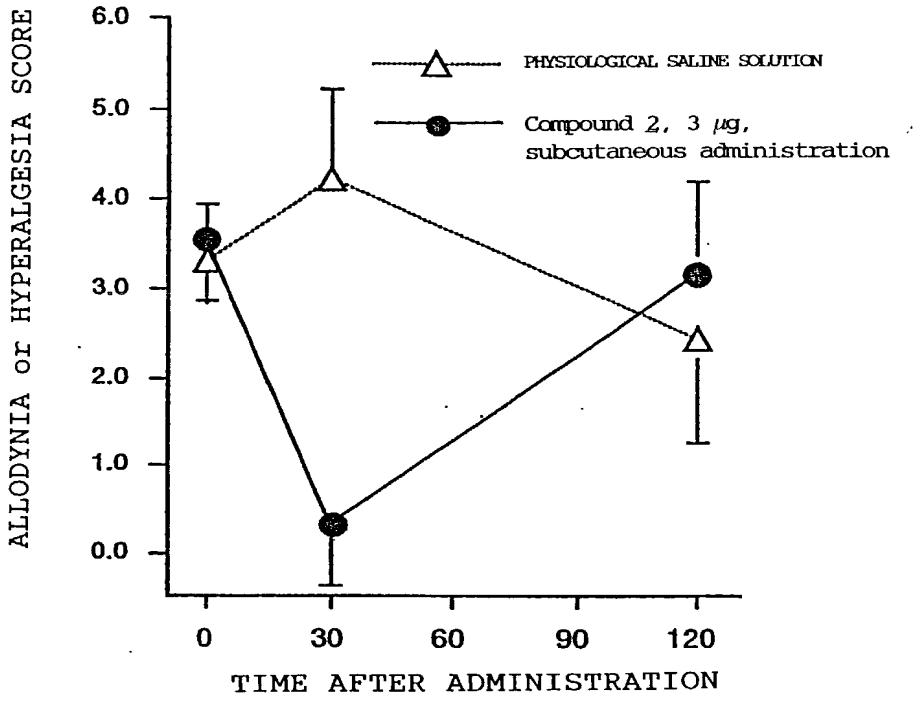
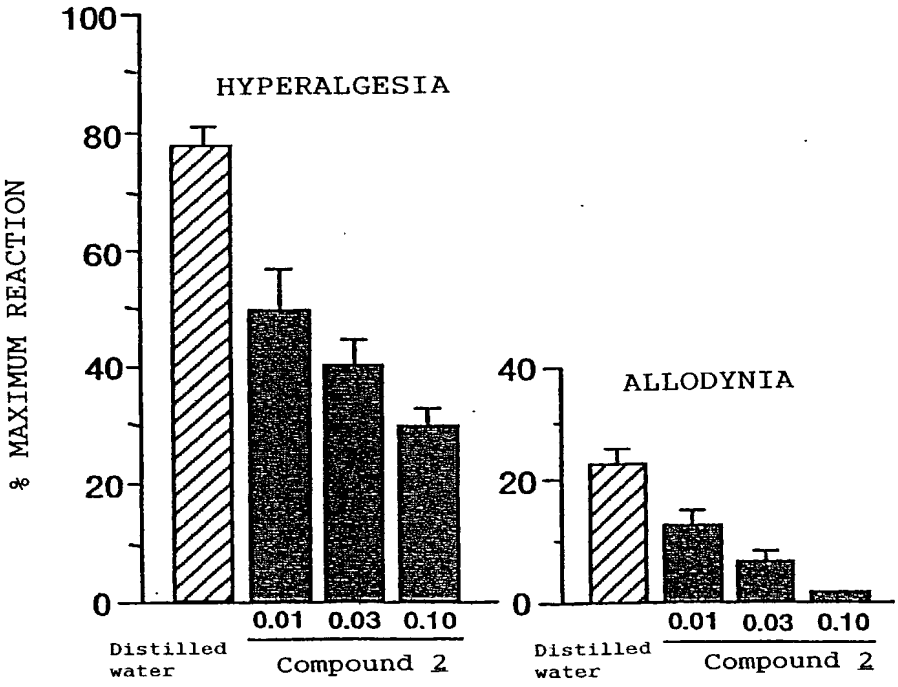


Fig. 8


% MAXIMUM REACTION
100
80
60
40
20
0
HYPERALGESIA
Distilled water
0.01
0.03
0.10
Compound 2
40
20
0
ALLODYNIA
Distilled water
0.01
0.03
0.10
Compound 2

Attorney Docket No. 1038-02

☐ Original Application

■ PCT National Application
U.S. Designated Office

☐ Continuation or Divisional Application

☐ Continuation-in-Part Application

**COMBINED DECLARATION,
POWER OF ATTORNEY AND PETITION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled REMEDIES FOR NEUROPATHIC PAIN AND MODEL ANIMALS OF NEUROPATHIC PAIN

☐ which is described in the specification and claims

☐ attached hereto.

☐ filed on _____

Application Serial No. _____

and was amended on _____
(if applicable)

■ which is described in International Application No. PCT/JP00/05690

filed 24 August 2000 and as amended on

_____ (if any),

which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

COMBINED DECLARATION, POWER OF ATTORNEY AND PETITION
(Page 2)

Attorney Docket No. 1038-02

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International Application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application(s) for patent or inventor's certificate or of any PCT International Application having a filing date before that of the application on which priority is claimed:

Number	Country	Date of Filing (day,month,year)	Priority Claimed
236778/99	Japan	24 August 1999	■ yes ☐ no
			☐ yes ☐ no
			☐ yes ☐ no
			☐ yes ☐ no
			☐ yes ☐ no

I hereby claim the benefit under Title 35, United States Code, §119(e) or §120 (as applicable) of any United States application(s) or §365(c) of any PCT International Application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International Application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112:

(Application Serial No.) *(Filing Date)* *(Status) (patented, pending, abandoned)*

(Application Serial No.) *(Filing Date)* *(Status) (patented, pending, abandoned)*

POWER OF ATTORNEY: As a named inventor, I hereby appoint the registered attorneys listed under **Customer No. 022469** and the following registered attorneys to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

T. Daniel Christenbury	Reg. No. 31,750	Frank A. Cona	Reg. No. 38,412
Guy T. Donatiello	Reg. No. 33,167	Michael A. Patané	Reg. No. 42,982
Paul A. Taufer	Reg. No. 35,703	Robert A. McKinley	Reg. No. 43,793
Albert T. Keyack	Reg. No. 32,906	Stewart M. Wiener	Reg. No. 46,201
Jeffrey L. Eichen	Reg. No. 41,496	Stephenie W. Yeung	Reg. No. 48,052
Austin R. Miller	Reg. No. 16,602		
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COMBINED DECLARATION, POWER OF ATTORNEY AND PETITION
(Page 3)

Attorney Docket No. 1038-02

I hereby petition for grant of a United States Letters Patent on this invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1. FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Hiroshi Nagase	Hiroshi Nagase	Feb. 20, 2002
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COMBINED DECLARATION, POWER OF ATTORNEY AND PETITION
(Page 4)

Attorney Docket No. 1038-02

8. FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
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POST OFFICE ADDRESS		

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RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

11. FULL NAME OF ADDITIONAL JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

12. FULL NAME OF ADDITIONAL JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

13. FULL NAME OF ADDITIONAL JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

14. FULL NAME OF ADDITIONAL JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
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